(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 August 2001 (23.08.2001)

PCT

(10) International Publication Number
WO 01/60818 A1

(51) International Patent Classification[7]: C07D 405/12, 307/52, C07C 233/58, A61K 31/443, 31/341, 31/167, A61P 3/10

(21) International Application Number: PCT/US00/03806

(22) International Filing Date: 14 February 2000 (14.02.2000)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicant: **TULARIK INC.** [US/US]; Two Corporate Drive, South San Francisco, CA 94080 (US).

(72) Inventors: **LI, Leping**; 2100 Davis Drive, Burlingame, CA 94010 (US). **MEDINA, Julio, Cesar**; 1407 Cedar Street, San Carlos, CA 94070 (US). **SHAN, Bei**; 349 Quay Lane, Redwood City, CA 94065 (US).

(74) Agents: **KEZER, William, B.** et al.; Townsend and Townsend and Crew LLP, 8th floor, Two Embarcadero Center, San Francisco, CA 94111 (US).

(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/60818 A1

(54) Title: LXR MODULATORS

(57) Abstract: The invention provides compounds, compositions and methods for modulating the effects of LXRα in a cell. The compounds and compositions are useful both as diagnostic indicators of LXRα function and as pharmacologically active agents. The compounds and compositions find particular use in the treatment of desease states associated with cholesterol metabolism, particularly artherosclerosis and hypercholesterolemia.

LXR MODULATORS

FIELD OF THE INVENTION

The present invention relates to compounds and methods useful for the modulation of LXR and to compositions which modulate the activity of LXR. In view of the activity of LXR in the control of cholesterol homeostasis, the compounds described herein are useful for lowering plasma cholesterol levels.

BACKGROUND

Cholesterol is used for the synthesis of bile acids in the liver, the manufacture and repair of cell membranes, and the synthesis of steroid hormones. There are both exogenous and endogenous sources of cholesterol. The average American consumes about 450 mg of cholesterol each day and produces an additional 500 to 1,000 mg in the liver and other tissues. Another source is the 500 to 1,000 mg of biliary cholesterol that is secreted into the intestine daily; about 50 percent is reabsorbed (enterohepatic circulation). Excess accumulation of cholesterol in the arterial walls can result in athersclerosis which is characterized by plaque formation. The plaques inhibit blood flow and promote clot formation, and can ultimately cause heart attacks, stroke and claudication. Development of therapeutic agents for the treatment of atherosclerosis and other diseases associated with cholesterol metabolism has been focused on achieving a more complete understanding of the biochemical pathways involved. Most recently, liver X receptors (LXRs) were identified as key components in cholesterol homeostasis.

The LXRs were first identified as orphan members of the nuclear receptor superfamily whose ligands and functions were unknown. Two LXR proteins α and β are known to exist in mammals. The expression of LXRα is restricted, with the highest levels being found in the liver, and lower levels found in kidney, intestine, spleen, and adrenals. See, Willy, *et al., Genes Dev.* **9(9):**1033-45 (1995). LXRβ is rather ubiquitous, being found in nearly all tissues examined. Recent studies on the LXRs indicate that they are activated by certain naturally occurring, oxidized derivatives of cholesterol, including 22(R)-hydroxycholesterol, 24(S)-hydroxycholesterol, and 24,25(S)-epoxycholesterol. See, Lehmann, *et al., J. Biol. Chem.* **272(6):**3137-3140 (1997). The expression pattern of LXRs and their oxysterol ligands provided the first hint that these receptors may play a role in cholesterol metabolism. See, Janowski, *et al., Nature* **383:**728-731 (1996).

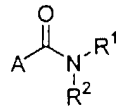
As noted above, cholesterol metabolism in mammals occurs via conversion into steroid hormones or bile acids. The role of LXRs in cholesterol homeostasis was first postulated to involve the pathway of bile acid synthesis, in which cholesterol 7α-hydroxylase (CYP7α) operates in a rate-limiting manner. Support for this proposal was provided when additional experiments found that the CYP7α promoter contained a functional LXR response element that could be activated by RXR/LXR heterodimers in an oxysterol- and retinoid-dependent manner.

Confirmation of LXR function as a transcriptional control point in cholesterol metabolism was made using knockout mice, particularly those lacking LXRα. See, Peet, *et al.*, *Cell* **93**:693-704 (1998). Mice lacking the receptor LXRα (*e.g.*, knockout or (-/-) mice) lost their ability to respond normally to increases in dietary cholesterol and were unable to tolerate any cholesterol in excess of that synthesized de novo. LXRα (-/-) mice did not induce transcription of the gene encoding CYP7α when fed diets containing additional cholesterol. This resulted in an accumulation of large amounts of cholesterol in the livers of LXRα (-/-) mice, and impaired hepatic function. These results further established the role of LXRα as the essential regulatory component of cholesterol homeostasis. LXRα is also believed to be involved in fatty acid synthesis. Accordingly, regulation of LXRα (*e.g.*, use of LXRα antagonists) could provide treatment for a variety of lipid disorders including obesity and diabetes.

In view of the importance of LXRs, and particularly LXRα to the delicate balance of cholesterol metabolism and fatty acid biosynthesis, we describe modulators of LXRs which are useful as therapeutic agents or diagnostic agents for the treatment of disorders associated with bile acid and cholesterol metabolism, including cholesterol gallstones, atherosclerosis, lipid storage diseases, obesity, and diabetes. The agents described herein are also useful for disease states associated with serum hypercholesterolemia, such as coronary heart disease.

SUMMARY OF THE INVENTION

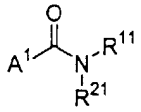
In one aspect, the present invention provides compositions for modulation of LXRα function in a cell. The compositions typically comprise a pharmaceutically acceptable excipient and a compound having the formula:



I

or a pharmaceutically acceptable salt thereof, in which the letter A represents substituted or unsubstituted forms of (C_5-C_{18})alkyl or (C_5-C_{18})heteroalkyl; the symbol R^1 represents substituted or unsubstituted forms of (C_3-C_{12})alkyl, (C_3-C_{12})heteroalkyl, aryl, heteroaryl, aryl(C_1-C_8)alkyl, heteroaryl(C_1-C_8)alkyl, aryl(C_2-C_8)heteroalkyl or heteroaryl(C_2-C_8)heteroalkyl; and the symbol R^2 represents substituted or unsubstituted forms of aryl, heteroaryl, aryl(C_1-C_8)alkyl, heteroaryl(C_1-C_8)alkyl, aryl(C_2-C_8)heteroalkyl or heteroaryl(C_2-C_8)heteroalkyl. Optionally, R^1 and R^2 are combined with the nitrogen atom to which each is attached, to form a 5-, 6-, 7- or 8-membered ring. Preferred compositions are those in which the compound above binds to the ligand binding domain of LXRα with an affinity of at least 1 micromolar.

A number of the compounds used in the present compositions are novel. Accordingly, the present invention provides, in another aspect, compounds having the formula:



II

or a pharmaceutically acceptable salt thereof, wherein the symbol A^1 represents substituted or unsubstituted forms of (C_5-C_{12})monocycloalkyl, (C_5-C_{12})heteromonocycloalkyl, (C_8-C_{18})bicycloalkyl, (C_8-C_{18})tricycloalkyl, (C_8-C_{18})heterobicycloalkyl or (C_8-C_{18})heterotricycloalkyl. The symbol R^{11} represents substituted or unsubstituted forms of (C_3-C_{12})alkyl, aryl, aryl(C_1-C_8)alkyl, aryl(C_2-C_8)heteroalkyl, (C_3-C_{12})heteroalkyl, heteroaryl, heteroaryl(C_1-C_8)alkyl or heteroaryl(C_2-C_8)heteroalkyl. The symbol R^{21} represents substituted or unsubstituted forms of an aryl, heteroaryl, aryl(C_1-C_8)alkyl, aryl(C_2-C_8)heteroalkyl, heteroaryl(C_1-C_8)alkyl or heteroaryl(C_2-C_8)heteroalkyl group. Additionally, R^{11} and R^{21} can be combined with the nitrogen atom to which each is attached to form a five- to eight-membered ring, with the following provisos:

when R^{21} is 2-pyridyl, R^{11} is other than a substituted or unsubstituted 2-(1-piperazinyl)ethyl or (tetrahydro-2H-pyrido[3,4-b]indol-2-yl)ethyl group;

when R^{21} is substituted or unsubstituted phenyl, R^{11} and R^{21} are not combined to form a ring with the attached nitrogen atom; and

when R^{21} is substituted or unsubstituted phenyl, R^{11} is not allyl, 2-(acylamino)ethyl, or benzyloxycarbonyl.

In yet another aspect, the present invention provides methods for modulating LXRα in a cell by administering to or contacting the cell with a composition containing a compound of Formula I above.

In still another aspect, the present invention provides methods for treating LXRα-responsive diseases by administering to a subject in need of such treatment, a composition containing a compound of Formula I. These methods are particularly useful for the treatment of pathology such as hypercholesterolemia, atherosclerosis, and hyperlipoproteinemia. In certain embodiments, the compound can be administered to the subject in combination with an additional hypercholesterolemic agent, for example, bile acid sequestrants, nicotinic acid, fibric acid derivatives or HMG CoA reductase inhibitors.

Certain compounds of the present invention are antiproliferative and can be used in compositions for treating diseases associated with abnormal cell proliferation (*e.g.*, cancer). Other diseases associated with an abnormally high level of cellular proliferation include restenosis, where vascular smooth muscle cells are involved, inflammatory disease states, where endothelial cells, inflammatory cells and glomerular cells are involved, myocardial infarction, where heart muscle cells are involved, glomerular nephritis, where kidney cells are involved, transplant rejection, where endothelial cells are involved, infectious diseases such as HIV infection and malaria, where certain immune cells and/or other infected cells are involved, and the like. Infectious and parasitic agents per se (*e.g.* bacteria, trypanosomes, fungi, *etc*) are also subject to selective proliferative control using the subject compositions and compounds.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain, or cyclic hydrocarbon radical, or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multi-radicals, having the number of carbon atoms designated (*i.e.* C_1-C_{10} means one to ten carbons). Examples of saturated hydrocarbon radicals include groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, (cyclohexyl)methyl, cyclopropylmethyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. The term "alkyl," unless otherwise noted, is also meant to include those derivatives of alkyl defined in more detail below

as "cycloalkyl" and "alkylene." The term "alkylene" by itself or as part of another substituent means a divalent radical derived from an alkane, as exemplified by -$CH_2CH_2CH_2CH_2$-. Typically, an alkyl group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the present invention. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms.

The term "alkoxy," employed alone or in combination with other terms means, unless otherwise stated, an alkyl group, as defined above, connected to the remainder of the molecule via an oxygen atom, such as, for example, methoxy, ethoxy, 1-propoxy, 2-propoxy and the higher homologs and isomers.

The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of the stated number of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N, Si and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any interior position of the heteroalkyl group. The heteroatom Si may be placed at any position of the heteroalkyl group, including the position at which the alkyl group is attached to the remainder of the molecule. Examples include -CH_2-CH_2-O-CH_3, -CH_2-CH_2-NH-CH_3, -CH_2-CH_2-N(CH_3)-CH_3, -CH_2-S-CH_2-CH_3, -CH_2-CH_2-S(O)-CH_3, -CH_2-CH_2-S(O)$_2$-CH_3 , -CH=CH-O-CH_3, -Si(CH_3)$_3$, -CH_2-CH=N-OCH_3, and -CH=CH-N(CH_3)-CH_3. Up to two heteroatoms may be consecutive, such as, for example, -CH_2-NH-OCH_3 and -CH_2-O-Si(CH_3)$_3$. Also included in the term "heteroalkyl" are those radicals described in more detail below as "heteroalkylene" and "heterocycloalkyl." The term "heteroalkylene" by itself or as part of another substituent means a divalent radical derived from heteroalkyl, as exemplified by -CH_2-CH_2-S-CH_2CH_2- and -CH_2-S-CH_2-CH_2-NH-CH_2-. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini. Still further, for alkylene and heteroalkylene linking groups, as well as all other linking groups described herein, no specific orientation of the linking group is implied.

The terms "cycloalkyl" and "heterocycloalkyl", by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl", respectively. The terms "cycloalkyl" and "heterocycloalkyl" are also meant to include bicyclic, tricyclic and polycyclic versions thereof. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, adamantyl, and the like.

Examples of heterocycloalkyl include 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, 1,4-diazabicyclo[2.2.2]oct-2-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like.

The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "fluoroalkyl," are meant to include monofluoroalkyl and polyfluoroalkyl.

The term "aryl," employed alone or in combination with other terms (*e.g.*, aryloxy, arylthioxy, arylalkyl) means, unless otherwise stated, an aromatic substituent which can be a single ring or multiple rings (up to three rings) which are fused together or linked covalently. The rings may each contain from zero to four heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. The aryl groups that contain heteroatoms may be referred to as "heteroaryl" and can be attached to the remainder of the molecule through a carbon atom or a heteroatom. Non-limiting examples of aryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl ring systems are selected from the group of acceptable substituents described below.

The terms "arylalkyl" and "arylheteroalkyl" are meant to include those radicals in which an aryl group is attached to an alkyl group (*e.g.*, benzyl, phenethyl, pyridylmethyl and the like) or a heteroalkyl group (*e.g.*, phenoxymethyl, 2-pyridyloxymethyl, 1-naphthyloxy-3-propyl, and the like). The arylalkyl and arylheteroalkyl groups will typically contain from 1 to 3 aryl moieties attached to the alkyl or heteroalkyl portion by a covalent bond or by fusing the ring to, for example, a cycloalkyl or heterocycloalkyl group. For arylheteroalkyl groups, a heteroatom can occupy the position at which the group is attached to the remainder of the molecule. For example, the term "arylheteroalkyl" is meant to include benzyloxy, 2-phenylethoxy, phenethylamine, and the like.

Each of the above terms (*e.g.*, "alkyl," "heteroalkyl" and "aryl") are meant to include both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be a variety of groups selected from: -OR', =O, =NR', =N-OR', -NR'R'', -SR', -halogen, -SiR'R''R''', -OC(O)R', -CO_2R', -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR"$C(O)_2$R', -NH-$C(NH_2)$=NH, -NR'$C(NH_2)$=NH, -NH-$C(NH_2)$=NR', -S(O)R', -$S(O)_2$R', -$S(O)_2$NR'R", -CN and -NO_2 in a number ranging from zero to (2N+1), where N is the total number of carbon atoms in such radical. R', R'' and R''' each independently refer to hydrogen, unsubstituted(C_1-C_8)alkyl and heteroalkyl, unsubstituted aryl, aryl substituted with 1-3 halogens, unsubstituted alkyl, alkoxy or thioalkoxy groups, or aryl-(C_1-C_4)alkyl groups. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 5-, 6-, or 7-membered ring. For example, -NR'R" is meant to include 1-pyrrolidinyl and 4-morpholinyl.

Similarly, substituents for the aryl groups are varied and are selected from: -halogen, -OR', -OC(O)R', -NR'R", -SR', -R', -CN, -NO_2, -CO_2R', -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR"$C(O)_2$R', -NH-$C(NH_2)$=NH, -NR'$C(NH_2)$=NH, -NH-$C(NH_2)$=NR', -S(O)R', -$S(O)_2$R', -$S(O)_2$NR'R", -N_3, -$CH(Ph)_2$, perfluoro(C_1-C_4)alkoxy, and perfluoro(C_1-C_4)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R' and R" are independently selected from hydrogen, (C_1-C_8)alkyl and heteroalkyl, unsubstituted aryl, (unsubstituted aryl)-(C_1-C_4)alkyl, and (unsubstituted aryl)oxy-(C_1-C_4)alkyl.

Two of the substituents on adjacent atoms of the aryl ring may optionally be replaced with a substituent of the formula -T-C(O)-$(CH_2)_q$-U-, wherein T and U are independently -NH-, -O-, -CH_2- or a single bond, and q is an integer of from 0 to 2. Alternatively, two of the substituents on adjacent atoms of the aryl ring may optionally be replaced with a substituent of the formula -A-$(CH_2)_r$-B-, wherein A and B are independently -CH_2-, -O-, -NH-, -S-, -S(O)-, -$S(O)_2$-, -$S(O)_2$NR'- or a single bond, and r is an integer of from 1 to 3. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl ring may optionally be replaced with a substituent of the formula -$(CH_2)_s$-X-$(CH_2)_t$-, where s and t are independently integers of from 0 to 3, and X is -O-, -NR'-, -S-, -S(O)-, -$S(O)_2$-, or -$S(O)_2$NR'-. The substituent R' in -NR'- and -$S(O)_2$NR'- is selected from hydrogen or unsubstituted (C_1-C_6)alkyl.

As used herein, the term "heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S) and silicon (Si).

The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, oxalic, maleic, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge, S.M., et al, "Pharmaceutical Salts", *Journal of Pharmaceutical Science*, **1977**, *66*, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

In addition to salt forms, the present invention provides compounds which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide a compound of formula I. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme.

Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

Certain compounds of the present invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers and individual isomers are all intended to be encompassed within the scope of the present invention.

The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

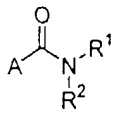
General

The present invention provides compositions, compounds and methods for modulating LXRα function in a cell. The compositions which are useful for this modulation will typically be those which contain an effective amount of an LXRα-modulating compound. In general, an effective amount of an LXRα-modulating compound is a concentration of the compound that will produce at 50 percent increase/decrease in LXRα activity in a cell-based reporter gene assay, or a biochemical peptide-sensor assay such as that described in co-pending applications Ser. Nos. 08/975,614 (filed November 21, 1997) and 09/163,713 (filed September 30, 1998).

Embodiments of the Invention

Compositions

In one aspect, the present invention provides compositions for modulation of LXRα function in a cell. The compositions typically comprise a pharmaceutically acceptable excipient and a compound having the formula:



I

or a pharmaceutically acceptable salt thereof, in which the letter A represents substituted or unsubstituted forms of (C_5-C_{18})alkyl or (C_5-C_{18})heteroalkyl. The symbol R^1 represents substituted or unsubstituted forms of (C_3-C_{12})alkyl, aryl, aryl(C_1-C_8)alkyl, aryl(C_2-C_8)heteroalkyl, (C_3-C_{12})heteroalkyl, heteroaryl, heteroaryl(C_1-C_8)alkyl or heteroaryl(C_2-C_8)heteroalkyl. The symbol R^2 represents substituted or unsubstituted forms of aryl, heteroaryl, aryl(C_1-C_8)alkyl, heteroaryl(C_1-C_8)alkyl, aryl(C_2-C_8)heteroalkyl or heteroaryl(C_2-C_8)heteroalkyl. Optionally, R^1 and R^2 can be combined with the nitrogen atom to which each is attached to form a 5-, 6-, 7- or 8-membered ring which may have from 0 to 2 additional heteroatoms as ring members. Examples of such rings include pyrrolidine, piperidine, morpholine, piperazine and the like. Preferred compositions are those in which the compound above binds to the ligand binding domain of LXRα with an affinity of at least 1 micromolar.

In certain preferred embodiments, A represents a substituted or unsubstituted form of a (C_5-C_{18})cycloalkyl or a (C_5-C_{18})heterocycloalkyl group, more preferably a (C_8-C_{18})bicycloalkyl, (C_8-C_{18})tricycloalkyl, (C_8-C_{18})heterobicycloalkyl or (C_8-C_{18})heterotricycloalkyl group. In particularly preferred embodiments, A represents a substituted or unsubstituted tricyclo[3.3.1.1^{3,7}]decanyl (or adamantyl), bicyclo[3.2.1]octanyl, bicyclo[5.2.0]nonanyl, bicyclo[4.3.2]undecanyl, tricyclo[2.2.1.0^{1}]heptanyl, tricyclo[5.3.1.1^{1}]dodecanyl, tricyclo[5.4.0.0^{2,9}]undecanyl, tricyclo[5.3.2.0^{4,9}]dodecanyl, tricyclo[4.4.1.1^{1,5}]dodecanyl or tricyclo[5.5.1.0^{3,11}]tridecanyl group. More preferably, A is a substituted or unsubstituted adamantyl group, most preferably an unsubstituted 1-adamantyl group.

Turning next to R^1, preferred embodiments are those in which R^1 is aryl(C_1-C_8)alkyl or heteroaryl(C_1-C_8)alkyl. More preferably, R^1 is branched heteroaryl(C_2-C_8)alkyl, for example, 1-(furan-2-yl)ethyl, 1-(pyridin-2-yl)ethyl, 1-(furan-2-yl)-2-propyl, 1-(2-pyridyl)-2-propyl, 1-(furanyl)isobutyl, 1-(3-pyridyl)isobutyl, 1-(pyridin-4-yl)ethyl, 1-(pyridin-4-yl)isobutyl, and the like. Most preferably, R^1 is 1-(furan-2-yl)ethyl or 1-(pyridin-2-yl)ethyl. In still other preferred embodiments, R^1 is a branched (C_3-C_8)alkyl, more preferably an isopropyl group. In yet other preferred embodiments, R^1 is a heteroaryl(C_3-C_8)alkenyl group. More preferably, R^1 is a 1-(3-furanyl)-3-butenyl group.

Returning to formula I above, the symbol R^2 is preferably a substituted or unsubstituted aryl or heteroaryl, more preferably a substituted or unsubstituted form of a pyridyl, phenyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, thiazolyl or furanyl group.

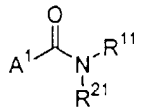
Still other preferred embodiments of the present compositions are those in which the compound of formula I has preferred combinations for A, R^1 and R^2. In one preferred group of combinations, A is adamantyl and R^1 is aryl(C_1-C_8)alkyl or heteroaryl(C_1-C_8)alkyl. In another preferred group of compounds, A is adamantyl, R^1 is aryl(C_1-C_8)alkyl or heteroaryl(C_1-C_8)alkyl, and R^2 is aryl or heteroaryl. In yet another preferred group of combinations, A is adamantyl, R^1 is branched heteroaryl(C_2-C_8)alkyl, and R^2 is aryl or heteroaryl. Still other preferred combinations are those in which A is adamantyl, R^1 is aryl(C_1-C_8)alkyl or heteroaryl(C_1-C_8)alkyl, and R^2 is pyridyl, phenyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, thiazolyl or furanyl.

Another group of preferred compounds for use in the present compositions are those in which A is substituted or unsubstituted adamantyl, R^1 is aryl(C_3-C_8)alkenyl or heteroaryl(C_3-C_8)alkenyl, and R^2 is a substituted or unsubstituted pyridyl or phenyl group. More preferably, the compounds are those in which A is unsubstituted 1-adamantyl, R^1 is phenyl(C_3-C_8)alkenyl or furanyl(C_3-C_8)alkenyl, and R^2 is a substituted or unsubstituted pyridyl or phenyl group. Most preferably, A is unsubstituted 1-adamantyl, R^1 is 1-(3-furanyl)-3-butenyl, and R^2 is a substituted or unsubstituted pyridyl or phenyl group. Preferred substituents for the phenyl or pyridyl group are small electron-withdrawing substituents, for example, halogen, halo(C_1-C_3)alkyl, nitro, cyano, and the like.

In another group of preferred compounds for use in the present compositions, A is substituted or unsubstituted adamantyl, R^1 is branched (C_3-C_8)alkyl, and R^2 is a substituted or unsubstituted pyridyl or phenyl group. More preferably, the compounds are those in which A is unsubstituted 1-adamantyl, R^1 is branched (C_3-C_8)alkyl, and R^2 is a substituted or unsubstituted pyridyl or phenyl group. Most preferably, A is unsubstituted 1-adamantyl, R^1 is isopropyl, and R^2 is a substituted or unsubstituted pyridyl or phenyl group. Preferred substituents for the phenyl or pyridyl group are small electron-withdrawing substituents, for example, halogen, halo(C_1-C_3)alkyl, nitro, cyano, and the like.

Compounds

A number of the compounds used in the present compositions are novel. Accordingly, the present invention provides, in another aspect, compounds having the formula:



II

or a pharmaceutically acceptable salt thereof, wherein the symbol A^1 represents substituted or unsubstituted forms of (C_5-C_{12})monocycloalkyl, (C_5-C_{12})heteromonocycloalkyl, (C_8-C_{18})bicycloalkyl, (C_8-C_{18})tricycloalkyl, (C_8-C_{18})heterobicycloalkyl or (C_8-C_{18})heterotricycloalkyl. The symbol R^{11} represents substituted or unsubstituted forms of (C_3-C_{12})alkyl, aryl, aryl(C_1-C_8)alkyl, aryl(C_2-C_8)heteroalkyl, (C_3-C_{12})heteroalkyl, heteroaryl, heteroaryl(C_1-C_8)alkyl or heteroaryl(C_2-C_8)heteroalkyl. The symbol R^{21} represents an aryl, heteroaryl, aryl(C_1-C_8)alkyl, heteroaryl(C_1-C_8)alkyl, aryl(C_2-C_8)heteroalkyl or heteroaryl(C_2-C_8)heteroalkyl group. Additionally, R^{11} and R^{21} can be combined with the nitrogen atom to which each is attached to form a five- to eight-membered ring, with the following provisos:

when R^{21} is 2-pyridyl, R^{11} is other than a substituted or unsubstituted 2-(1-piperazinyl)ethyl or (tetrahydro-2H-pyrido[3,4-b]indol-2-yl)ethyl group;

when R^{21} is substituted or unsubstituted phenyl, R^{11} and R^{21} are not combined to form a ring with the attached nitrogen atom; and

when R^{21} is substituted or unsubstituted phenyl, R^{11} is not allyl, 2-(acylamino)ethyl, or benzyloxycarbonyl.

In formula II above, A^1 is preferably a substituted or unsubstituted form of (C_8-C_{18})bicycloalkyl, (C_8-C_{18})tricycloalkyl, (C_8-C_{18})heterobicycloalkyl or (C_8-C_{18})heterotricycloalkyl, more preferably, (C_8-C_{18})tricycloalkyl or (C_8-C_{18})heterotricycloalkyl. Still more preferably, A^1 is a substituted or unsubstituted form of (C_8-C_{18})tricycloalkyl, with substituted or unsubstituted adamantyl being most preferred.

Preferred groups for R^{11} are aryl(C_1-C_8)alkyl and heteroaryl(C_1-C_8)alkyl. More preferably, R^{11} is branched heteroaryl(C_2-C_8)alkyl, for example, 1-(furan-2-yl)ethyl, 1-(pyridin-2-yl)ethyl, 1-(furan-2-yl)-2-propyl, 1-(2-pyridyl)-2-propyl, 1-(furanyl)isobutyl, 1-(3-pyridyl)isobutyl, 1-(pyridin-4-yl)ethyl, 1-(pyridin-4-yl)isobutyl, 1-(2-furanyl)-3-butenyl, 1-(3-furanyl)-3-butenyl and the like. Most preferably, R^{11} is 1-(furan-2-yl)ethyl, 1-(3-furanyl)-3-butenyl or 1-(pyridin-2-yl)ethyl.

Preferred groups for R^{21} include aryl or heteroaryl, more preferably substituted or unsubstituted forms of pyridyl, phenyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, thiazolyl or furanyl.

As with the compounds used in the compositions above, certain combinations of substituents represent particularly preferred embodiments of the invention. For example, when A^1 is adamantyl, R^{11} is preferably aryl(C_1-C_8)alkyl or heteroaryl(C_1-C_8)alkyl, and R^{21} is preferably aryl or heteroaryl. Still more preferred are those combinations in which R^{11} is branched heteroaryl(C_2-C_8)alkyl, and R^{21} is aryl or heteroaryl. Still other preferred compounds are those in which A^1 is adamantyl, R^{11} is aryl(C_1-C_8)alkyl or heteroaryl(C_1-C_8)alkyl, and R^{21} is pyridyl, phenyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, thiazolyl or furanyl.

Still other preferred compounds are those in which A^1 is substituted or unsubstituted adamantyl, R^{11} is aryl(C_3-C_8)alkenyl or heteroaryl(C_3-C_8)alkenyl, and R^{21} is a substituted or unsubstituted pyridyl or phenyl group. More preferably, the compounds are those in which A^1 is unsubstituted 1-adamantyl, R^{11} is phenyl(C_3-C_8)alkenyl or furanyl(C_3-C_8)alkenyl, and R^{21} is a substituted or unsubstituted pyridyl or phenyl group. Most preferably, A^1 is unsubstituted 1-adamantyl, R^{11} is 1-(3-furanyl)-3-butenyl, and R^{21} is a substituted or unsubstituted pyridyl or phenyl group. Preferred substituents for the phenyl or pyridyl group are small electron-withdrawing substituents, for example, halogen, halo(C_1-C_3)alkyl, nitro, cyano, and the like.

In another group of preferred compounds for use in the present compositions, A^1 is substituted or unsubstituted adamantyl, R^{11} is branched (C_3-C_8)alkyl, and R^{21} is a substituted or unsubstituted pyridyl or phenyl group. More preferably, the compounds are those in which A^1 is unsubstituted 1-adamantyl, R^{11} is branched (C_3-C_8)alkyl, and R^{21} is a substituted or unsubstituted pyridyl or phenyl group. Most preferably, A^1 is unsubstituted 1-adamantyl, R^{11} is isopropyl, and R^{21} is a substituted or unsubstituted pyridyl or phenyl group. Preferred substituents for the phenyl or pyridyl group are small electron-withdrawing substituents, for example, halogen, halo(C_1-C_3)alkyl, nitro, cyano, and the like.

Methods

In yet another aspect, the present invention provides methods for modulating the action of LXRα in a cell. According to this method, the cell is contacted with a sufficient concentration of a composition containing a compound of formula I, above, for either an agonistic or antagonistic effect to be detected.

In still another aspect, the present invention provides methods for the treatment of pathology such as hypercholesterolemia, atherosclerosis, and hyperlipoproteinemia using pharmaceutical compositions containing compounds of the foregoing description of the general Formula I. Briefly, this aspect of the invention involves administering to a patient an effective formulation of one or more of the subject compositions. In other embodiments, the compound of Formula I can be administered in combination with other hypercholesterolemic agents (*e.g.*, a bile acid sequestrant, nicotinic acid, fibric acid derivatives or HMG CoA reductase inhibitors), or in combination with other agents that affect cholesterol or lipid metabolism.

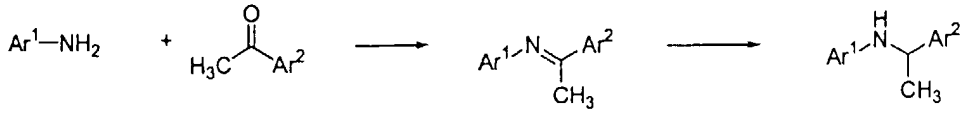
Preferred compounds and compositions for use in the present methods are those which have been described in the preceding sections.

Synthesis

Compounds of the present invention can be prepared using readily available starting materials or known intermediates. In general, the compounds are prepared from a carboxylic acid (or activated form thereof) of the formula A-CO_2H and a secondary amine of the formula R^1-NH-R^2 using known coupling procedures. A number of monocyclic, bicyclic and tricyclic alkane carboxylic acids are commercially available, including, for example, 1-adamantanecarboxylic acid, 3-noradamantanecarboxylic acid, 5-norbornene-2-carboxylic acid, and 1-methyl-1-cyclohexanecarboxylic acid.

Amines which are useful in forming the compound and compositions of the present invention are also readily accessible either through commercial sources or via chemical synthesis. For example, an arylamine (Ar^1-NH_2) can be condensed with an aryl ketone (*e.g.*, $CH_3C(O)Ar^2$) to yield an imine which can then be reduced to provide a suitable disubstituted amine (see Scheme 1). In some instances the intermediate imine can be converted to the amine *in situ*.

Scheme 1



One of skill in the art will understand that the above reaction scheme can also be used with, for example, nonaromatic amines and aldehydes or other ketones. An alternative method to the reductive amination procedure outlined above is described in the Examples section below.

Regardless of the source or procedure used to obtain a suitable amine component, coupling of the amine to an appropriate carboxylic acid, carboxylic acid chloride, or activated ester is straightforward and can be accomplished using standard procedures.

Some of the compounds of Formula I may exist as stereoisomers, and the invention includes all active stereoisomeric forms of these compounds. In the case of optically active isomers, such compounds may be obtained from corresponding optically active precursors using the procedures described above or by resolving racemic mixtures. The resolution may be carried out using various techniques such as chromatography, repeated recrystallization of derived asymmetric salts, or derivatization, which techniques are well known to those of ordinary skill in the art.

The compounds of the invention may be labeled in a variety of ways. For example, the compounds may contain radioactive isotopes such as, for example, ^{3}H (tritium) and ^{14}C (carbon-14). Similarly, the compounds may be advantageously joined, covalently or noncovalently, directly or through a linker molecule, to a wide variety of other compounds, which may provide pro-drugs or function as carriers, labels, adjuvents, coactivators, stabilizers, *etc.* Such labeled and joined compounds are contemplated within the present invention.

Analysis of compounds

Representative compounds and compositions were demonstrated to have pharmacological activity in *in vitro* and cell culture assays, *e.g.*, they are capable of specifically modulating a cellular physiology to reduce an associated pathology or provide or enhance a prophylaxis.

Certain preferred compounds and compositions are capable of specifically regulating LXRα. Compounds may be evaluated *in vitro* for their ability to activate LXRα receptor function using cell-based assays such as that described in Lehmann, et al. (*J. Biol. Chem.* **1997**, *272(6),* 3137-3140) or biochemical assays (see co-pending applications Ser. Nos. 08/975,614 (filed November 21, 1997) and 09/163,713 (filed September 30, 1998)). Alternatively, the compounds and compositions can be evaluated for their ability to increase or decrease gene expression modulated by LXR, using western-blot analysis. Established animal models to evaluate hypocholesterolemic effects of compounds are known in the art. For example, compounds disclosed herein can be tested for their ability to lower cholesterol levels in hamsters fed a high-cholesterol diet, using a protocol similar to that described in Spady et al. *(J. Clin. Invest.* **1988**, *81*, 300), Evans et al. (*J. Lipid Res.* **1994**, *35*, 1634), and Lin et al *(J. Med. Chem.* **1995**, *38*, 277). Still further, LXRα animal models (*e.g.*,

LXRα (+/-) and (-/-) mice) can be used for evaluation of the present compounds and compositions (see, for example, Peet, et al. *Cell* 1998, *93*, 693-704).

Formulation and administration of compounds and pharmaceutical compositions

The invention provides methods of using the subject compounds and compositions to treat disease or provide medicinal prophylaxis, to activate LXR receptor function in a cell, to reduce blood cholesterol concentration in a host, to slow down and/or reduce the abnormal cellular proliferation including the growth of tumors, *etc.* These methods generally involve contacting the cell or cells with or administering to a host an effective amount of the subject compounds or pharmaceutically acceptable compositions.

The compositions and compounds of the invention and the pharmaceutically acceptable salts thereof can be administered in any effective way such as via oral, parenteral or topical routes. Generally, the compounds are administered in dosages ranging from about 2 mg up to about 2,000 mg per day, although variations will necessarily occur depending on the disease target, the patient, and the route of administration. Preferred dosages are administered orally in the range of about 0.05 mg/kg to about 20 mg/kg, more preferably in the range of about 0.05 mg/kg to about 2 mg/kg, most preferably in the range of about 0.05 mg/kg to about 0.2 mg per kg of body weight per day.

In one embodiment, the invention provides the subject compounds combined with a pharmaceutically acceptable excipient such as sterile saline or other medium, water, gelatin, an oil, *etc.* to form pharmaceutically acceptable compositions. The compositions and/or compounds may be administered alone or in combination with any convenient carrier, diluent, *etc.* and such administration may be provided in single or multiple dosages. Useful carriers include solid, semi-solid or liquid media including water and non-toxic organic solvents.

In another embodiment, the invention provides the subject compounds in the form of a pro-drug, which can be metabolically converted to the subject compound by the recipient host. A wide variety of pro-drug formulations are known in the art.

The compositions may be provided in any convenient form including tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, suppositories, *etc.* As such the compositions, in pharmaceutically acceptable dosage units or in bulk, may be incorporated into a wide variety of containers. For example, dosage units may be included in a variety of containers including capsules, pills, *etc.*

The compositions may be advantageously combined and/or used in combination with other hypocholesterolemic therapeutic or prophylactic agents,

different from the subject compounds. In some instances, administration in conjunction with the subject compositions enhances the efficacy of such agents (i.e., there is a synergistic effect between the agents used in combination). Exemplary hypocholesterolemic and/or hypolipemic agents include: bile acid sequestrants such as quaternary amines (*e.g.* cholestyramine and colestipol); nicotinic acid and its derivatives; HMG-CoA reductase inhibitors such as mevastatin, pravastatin, and simvastatin; gemfibrozil and other fibric acids, such as clofibrate, fenofibrate, benzafibrate and cipofibrate; probucol; raloxifene and its derivatives; and mixtures thereof.

The compounds and compositions also find use in a variety of *in vitro* and *in vivo* assays, including diagnostic assays. For example, various allotypic LDL receptor gene expression processes may be distinguished in sensitivity assays with the subject compounds and compositions, or panels thereof. In certain assays and in *in vivo* distribution studies, it is desirable to used labeled versions of the subject compounds and compositions, *e.g.* radioligand displacement assays. Accordingly, the invention provides the subject compounds and compositions comprising a detectable label, which may be spectroscopic (*e.g.* fluorescent), radioactive, *etc.*

The following examples are offered by way of illustration and not by way of limitation.

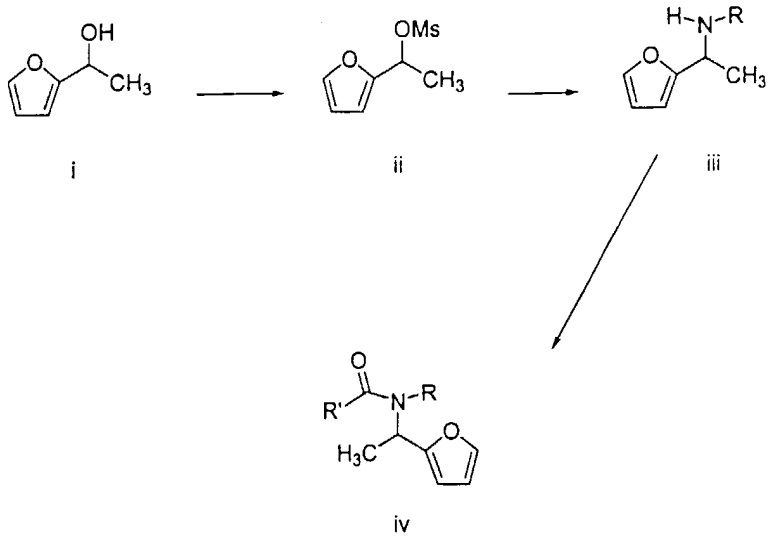
EXAMPLES

^{1}H-NMR spectra were recorded on a Varian Gemini 400 MHz NMR spectrometer. Significant peaks are tabulated in the order: number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br s, broad singlet) and coupling constant(s) in Hertz. Electron Ionization (EI) mass spectra were recorded on a Hewlett Packard 5989A mass spectrometer. Mass spectrometry results are reported as the ratio of mass over charge, followed by the relative abundance of each ion (in parentheses). Abbreviations used in the examples below have their accepted meanings in the chemical literature. For example, THF (tetrahydrofuran), LDA (lithium diisopropylamide), MeCN (acetonitrile), and DMAP (4-dimethyaminopyridine).

The compounds provided in Examples 1-8 were synthesized using the general scheme provided below (Scheme 2) for the preparation of 1-(2-furanyl)-ethylamine derivatives. The compounds provided in Examples 9 and 10 were prepared using similar methods. Suitable alteration of the various components in Scheme 2, including the secondary mesylate (**ii**), the amine used to displace the mesylate (to form **iii**), or the acyl chloride (used in the final step) provide entry into

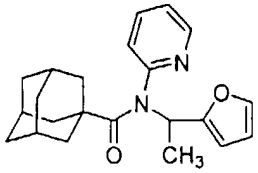
a wide variety of compounds of the present invention. As provided in the scheme, a suitable alcohol (**i**), preferably a primary or secondary alcohol, can be converted to a leaving group (*e.g.*, a mesylate ester with the addition of methanesulfonylchloride) to provide an intermediate such as **ii**. Treatment of **ii** with a primary amine such as R-NH_2 provides the amine derivative **iii**. Subsequent acylation of the secondary amine functional group present in **iii** with acylating agents (R^1-COCl) provides the target compounds **iv**.

Scheme 2



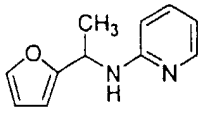
EXAMPLE 1

This example illustrates the preparation of Compound **1**.



1

1.1 Preparation of intermediate 2-(1-(furan-2-yl)ethyl)aminopyridine (1.1)



1.1

(±)-1-(2-furyl)ethanol (10.8 g, 95.4 mmol) was dissolved in THF (264 mL) under N_2 at ambient temperature. To the mixture was added LDA (52.5 mL of a 2.0 M solution in heptane/THF, 105 mmol, from Aldrich Chemical Co.) dropwise at -45°C (dry ice/MeCN bath) over a period of 12 min. The mixture was stirred at -45°C for 2 hours. Methanesulfonyl chloride (9.0 mL, 115 mmol) was added dropwise at -45°C for 10 min. The mixture was stirred at -45°C for 2 h, then a solution of 2-aminopyridine (15.7 g, 167 mmol) in THF (36ml) was added dropwise at -45°C over 15 min. The resulting mixture was quenched with water, extracted with $CHCl_3$, and the organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed by evaporation and the crude product was purified by column chromatography on silica gel to afford the title compound as an oil in 51.8% yield.

^{1}H-NMR ($CDCl_3$ 400 MHz) δ 8.1 (d, J=4.76 Hz, 1H), 7.44-7.34 (m, 2H), 6.59 (dd, J=5.12, 7.2 Hz, 1H), 6.40 (d, J=8 Hz, 1H), 6.30 (m, 1H), 6.17 (d, J=3.16 Hz, 1H), 5.04 (m, 1H), 4.85 (m, 1H), 1.58 (d, J=6.64 Hz, 3H).

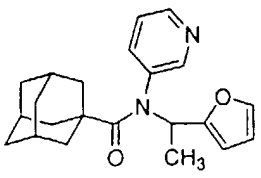
1.2 Preparation of Compound 1

To (1-furan-2-yl-ethyl)-pyridin-2-yl-amine (2.82 g, 15.0 mmol) in pyridine (24.2 mL) was added in one portion 1-adamantanecarbonyl chloride (9.40 g, 44.9 mmol) and DMAP (92 mg, 0.753 mmol) under N_2 at ambient temperature. The reaction mixture was heated to reflux for 1.5 h, then allowed to cool, quenched with H_2O, and extracted with $CHCl_3$. The organic layer was washed with brine and dried over $MgSO_4$. The solvent was evaporated and the crude product was purified by recrystallizing from ethyl acetate/ hexanes to afford 3.67 g of title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.49 (m, 1H), 6.57 (d, J=7.96 Hz, 1H), 6.22 (d, J=1.89 Hz, 1H), 6.09 (m, 1H), 5.98 (m, 1H), 1.95-1.40 (m, 18H).

EXAMPLE 2

This example illustrates the preparation of Compound **2**.



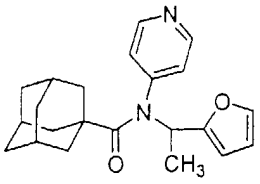
2

The title compound was prepared in a manner analogous to that described for the compound of Example 1.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.52 (d, J=4.4 Hz, 1H), 8.10 (br s, 1H), 7.35 (d, J=1.8 Hz, 1H), 7.20 (m, 1H), 7.05 (m, 1H), 6.22 (m, 2H), 5.93 (m, 1H), 1.84 (m, 2H), 1.72 (m, 6H), 1.56 (m, 3H), 1.45 (m, 3H), 1.34 (d, J=7 Hz, 3H).

EXAMPLE 3

This example illustrates the preparation of Compound **3**.



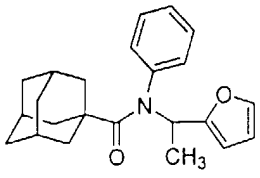
3

The title compound was prepared in a manner analogous to that described for the compound of Example 1.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.52 (d, J=2 Hz, 2H), 7.37 (s, 1H), 6.15 (m, 1H), 5.95 (d, J=3.28 Hz, 1H), 1.87–1.33 (m, 18H).

EXAMPLE 4

This example illustrates the preparation of Compound **4**.



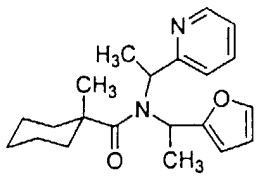
4

The title compound was prepared in a manner analogous to that described for the compound of Example 1.

^{1}H-NMR ($CDCl_3$, 400Mhz) δ 7.34-7.20 (m, 5H), 6.8 (br s, 1H), 6.20 (m, 2H), 5.89 (m, 1H), 1.82-1.30 (m, 18H).

EXAMPLE 5

This example illustrates the preparation of Compound **5**.

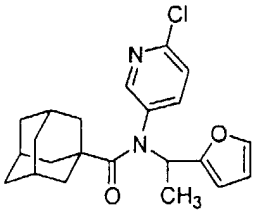


5

The title compound was prepared in a manner analogous to that described for the compound of Example 1. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.49 (m, 1H), 7.52 (m, 1H), 7.35 (m, 1H), 7.20 (m, 1H), 6.57 (m, 1H) 6.23 (m, 1H), 6.15 (m, 1H), 6.00 (m, 1H), 1.90-0.80 (m, 16H).

EXAMPLE 6

This example illustrates the preparation of Compound **6**.

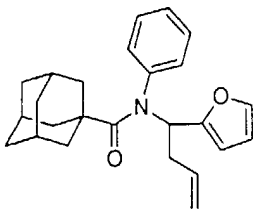


6

The title compound was prepared using methods outlined above. ^{1}H NMR ($CDCl_3$) δ 7.81 (broad s, 1H), 7.36 (s, 1H), 7.21 (d, J = 8.4 Hz, 1H), 6.95 (broad s, 1H), 6.21 (m, 2H), 5.95 (m, 1H), 1.88 (m, 3H), 1.70 (m, 6H), 1.60 (d, J=12 Hz, 3H), 1.48 (d, J=12 Hz, 3H), 1.33 (d, J=7 Hz, 3H). MS (ES+): 385 (M+H, 100). Anal. Calcd. for $C_{22}H_{25}ClN_2O_2$: C, 68.65; H, 6.55; N, 7.28; Cl, 9.21. Found: C, 68.37; H, 6.56; N, 7.18; Cl, 9.46.

EXAMPLE 7

This example illustrates the preparation of Compound 7.



7

Step 7a.

To a stirred solution of sodium docecylsulfate (12 mL, 35 mM in water) and scandium trifluoromethanesulfonate [$Sc(OTf)_3$, 214 mg) were added aniline (0.19 mL, 2.06 mmol), allyltributylstannane (0.94 mL, 3.01 mmol), and 2-furaldehyde (0.215 mL, 2.59 mmol) successively, and the mixture was stirred at room temperature. After 24 h, the mixture was diluted with water and ethyl acetate. After separation of layers, the organic layer was washed with saturated $NaHCO_3$ twice, dried over $MgSO_4$, filtered, ad concentrated. The crude product was purified by flash chromatography on silica gel eluted with hexane/ethyl acetate (20:1) to give 0.360g of the desired homoallylic amine in 81.9% yield.

^1H NMR ($CDCl_3$) δ 7.35 (s, 1H), 7.15 (t, J = 6.8 Hz, 2H), 6.72 (t, J = 6.8 Ha, 1H), 6.61 (d, J = 6.8 HZ, 2H), 6.30 (d, J = 1.8 Hz, 1H), 6.18 (d, J = 1.8 Hz, 1H), 5.75 (m, 1H), 5.18 (d, J = 18 Hz, 1H), 5.12 (d, J = 10 Hz, 1H), 4.55 (m, 1H), 4.0 (bs, 1H), 2.66 (m, 1H).

Step 7b.

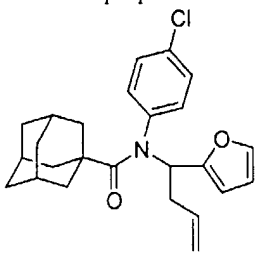
The mixture of 1-adamantanecarbonyl chloride (293 mg, 1.48 mmol), the above aniline (158 g, 0.74 mmol), 4-dimethylaminopyridine (DMAP, 30 mg, 0.25 mmol) in pyridine (2 mL) was heated at 90°C for 3 days. The reaction mixture was diluted with ethyl acetate, washed with 1 N HCl (2X) and brine. The organic layer was dried over $MgSO_4$, filtered and stripped. The crude product was purified by flash chromatography on silica gel eluted with hexane/ethyl acetate (20:1) to give 80 mg of the title compound in 28.8% yield (along with recovered starting aniline).

^1H NMR (CD_3OD) δ 7.44 (s, 1H), 7.35 (m, 2H), 6.90 (m, 2H), 6.25 (d, J = 4.8 Hz, 1H), 6.17 (t, J = 7.7 Hz, 2H), 5.99 (d, J = 4.8 Hz, 1H), 5.83 (m, 1H),

5.18 (d, J = 18 Hz, 1H), 5.06 (d, J = 12 Hz, 1H), 2.50 (t, J = 4.8 Hz, 2H), 1.79 (bs, 3H), 1.75 (d, J = 12 Hz, 3H), 1.68 (d, J = 12 Hz, 3H), 1.52 (d, J = 12 Hz, 3H), 1.43 (d, J = 12 Hz, 3H). MS (ES+): 376 (M+H, 100). Anal. Calcd. for $C_{25}H_{29}NO_2$: C, 79.96; H, 7.78; N, 3.73. Found: C, 79.79; H, 7.86; N, 3.62.

EXAMPLE 8

This example illustrates the preparation of Compound **8**.



8

Step 8a:

Following the procedures described for Example 7 and substituting 4-chloroaniline for aniline, in Step 7a, the corresponding N-4-chlorophenylhomoallylamine was obtained, 0.448 g, 90.0%.

^{1}H NMR ($CDCl_3$) δ 7.34 (s, 1H), 7.08 (d, J = 6.8 Hz, 2H), 6.52 (d, J = 6.8 Hz, 2H), 6.29 (d, J = 3.2 Hz, 1H), 6.13 (d, J = 3.2Hz, 1H), 5.75 (m, 1H), 5.18 (d, J = 18 Hz, 1H), 5.13 (d, J = 9.2 Hz, 1H), 4.50 (m, 1H), 3.99 (bs, 1H), 2.64 (m, 2H).

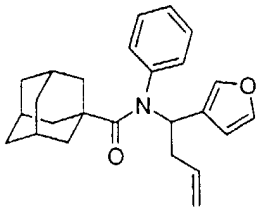
Step 8b:

Following conditions described in Step 7b and substituting the corresponding aniline with the 4-chlorosubstituted aniline from Step 8a, the title compound was obtained.

^{1}H NMR ($CDCl_3$) δ 7.30 (s, 1H), 7.00-7.30 (m, 4H), 6.21 (d, J = 3.3 Hz, 1H), 6.20 (t, J = 4.8 Hz, 1H), 5.95 (d, J = 3.3Hz, 1H), 5.78 (m, 1H), 5.13 (d, J = 18 Hz, 1H), 5.08 (d, J = 12 Hz, 1H), 2.44 (m, 2H), 1.83 (bs, 3H), 1.73 (d, J = 12 Hz, 3H), 1.69 (d, J = 12 Hz, 3H), 1.56 (d, J = 12 Hz, 3H), 1.46 (d, J = 12 Hz, 3H). MS (ES+): 410 (M+H, 100). Anal. Calcd. for $C_{25}H_{28}ClNO_2$: C, 73.25; H, 6.88; N, 3.42. Found: C, 73.27; H, 6.94; N, 3.34.

EXAMPLE 9

This example illustrates the preparation of Compound **9**.



9

Step 9a:

Following the procedures described for Example 7 and substituting 3-furaldehyde for 2-furaldehyde in Step 7a, the corresponding 3-furylhomoallylamine was obtained, 0.32 g, 66.0% yield.

^{1}H NMR ($CDCl_3$) δ 7.35 (bs, 1H), 7.32 (s, 1H), 7.04 (t, J = 7.2 Hz, 2H), 6.70 (t, J = 7.2 Hz, 1H), 6.60 (d, J = 7.2 Hz, 2H), 6.36 (s, 1H), 5.80 (m, 1H), 5.16 (d, J = 16Hz, 1H), 5.12 (d, J = 12 Hz, 1H), 4.48 (m, 1H), 3.90 (bs, 1H), 2.52 (m, 2H). MS (ES+): 214 (M+H, 100).

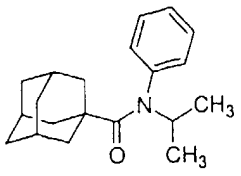
Step 9b:

Following conditions described in Step 7b and substituting the corresponding aniline with the aniline from Step 9a, the title compound was obtained in 28.3% yield.

^{1}H NMR ($CDCl_3$) δ 7.25-7.35 (m, 6H), 7.09 (s, 1H), 6.13 (s, 1H), 6.01 (t, J = 6.0 Hz, 1H), 5.80 (m, 1H), 5.11 (d, J = 18 Hz, 1H), 5.05 (d, J = 12 Hz, 1H), 2.51 (m, 1H), 2.35 (m, 1H), 1.79 (bs, 3H), 1.68 (bs, 6H), 1.54 (d, J = 12 Hz, 3H), 1.44 (d, J = 12 Hz, 3H). MS (ES+): 376(M+H, 100). Anal. Calcd. for $C_{25}H_{29}NO_2$: C, 79.96; H, 7.78; N, 3.73. Found: C, 79.89; H, 7.82; N, 3.72.

EXAMPLE 10

This example illustrates the preparation of Compound **10**.



10

Following conditions described in Step 7b and substituting the aniline with isopropylamine, the title compound was obtained in 40% yield.

^{1}H NMR ($CDCl_3$) δ 7.35 (m, 3H), 7.11 (m, 2H), 4.92 (m, 1H), 1.79 (bs, 3H), 1.68 (bs, 6H), 1.53 (d, J = 12 Hz, 3H), 1.48 (d, J = 12 Hz, 3H), 0.98 (d, J = 6.8 Hz, 6H). MS (ES+): 298(M+H), 100.

EXAMPLE 11

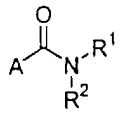
In order to identify agonists for LXRα, a cell-based high throughput screen was developed. Briefly, a DNA-binding domain of the nonreceptor transcription factor GAL4 was fused to the putative ligand-binding domain of LXRα. The resulting construct was introduced into 293 cells, together with an UAS-containing luciferase reporter construct. The transfected cells were then treated with the compounds and luciferase activity was measured. Individual compounds were evaluated relative to a control (no additional compound) at a concentration of 10 μM. Relative luciferase activity is provided below for five of the compounds described in the Examples above (luciferase activity of the control was assigned a value of 1).

Example	Relative Activity
Example 1	4
Example 2	5
Example 3	≥10
Example 4	3
Example 5	≥10

All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

WHAT IS CLAIMED IS

1. A composition for modulation of LXR function in a cell, said composition comprising a pharmaceutically acceptable excipient and a compound having the formula:



or a pharmaceutically acceptable salt thereof, wherein

A is a member selected from the group consisting of (C_5-C_{18})alkyl and (C_5-C_{18})heteroalkyl;

R^1 is a member selected from the group consisting of (C_3-C_{12})alkyl, aryl, aryl(C_1-C_8)alkyl, aryl(C_2-C_8)heteroalkyl, (C_3-C_{12})heteroalkyl, heteroaryl, heteroaryl(C_1-C_8)alkyl and heteroaryl(C_2-C_8)heteroalkyl; and

R^2 is a member selected from the group consisting of aryl, heteroaryl, aryl(C_1-C_8)alkyl, heteroaryl(C_1-C_8)alkyl, aryl(C_2-C_8)heteroalkyl and heteroaryl(C_2-C_8)heteroalkyl;

wherein R^1 and R^2 are optionally combined together with the nitrogen atom to which each is attached to form a 5-, 6-, 7- or 8-membered ring, and said compound binds to the ligand binding domain of LXRα with an affinity of at least 1 micromolar.

2. A composition in accordance with claim 1, wherein A is selected from the group consisting of (C_5-C_{18})cycloalkyl and (C_5-C_{18})heterocycloalkyl.

3. A composition in accordance with claim 1, wherein A is selected from the group consisting of (C_8-C_{18})bicycloalkyl, (C_8-C_{18})tricycloalkyl, (C_8-C_{18})heterobicycloalkyl and (C_8-C_{18})heterotricycloalkyl.

4. A composition in accordance with claim 1, wherein A is adamantyl.

5. A composition in accordance with claim 3, wherein R^1 is selected from aryl(C_1-C_8)alkyl and heteroaryl(C_1-C_8)alkyl.

6. A composition in accordance with claim 3, wherein R^2 is selected from aryl and heteroaryl.

7. A composition in accordance with claim **1**, wherein A is adamantyl, R^1 is selected from aryl(C_1-C_8)alkyl and heteroaryl(C_1-C_8)alkyl and R^2 is selected from aryl and heteroaryl.

8. A composition in accordance with claim **1**, wherein A is adamantyl, R^1 is selected from heteroaryl(C_3-C_8)alkenyl and R^2 is selected from phenyl and pyridyl.

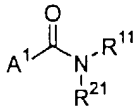
9. A composition in accordance with claim **1**, wherein A is adamantyl, R^1 is selected from branched (C_3-C_8)alkyl and R^2 is selected from phenyl and pyridyl.

10. A composition in accordance with claim **1**, wherein A is adamantyl, R^1 is heteroaryl(branched C_2-C_8)alkyl and R^2 is selected from aryl and heteroaryl.

11. A composition in accordance with claim **1**, wherein A is adamantyl, R^1 is 1-(heteroaryl)-(C_2-C_8)alkyl and R^2 is selected from aryl and heteroaryl.

12. A composition in accordance with claim **1**, wherein A is 1-adamantyl, R^1 is selected from aryl(C_1-C_8)alkyl and heteroaryl(C_1-C_8)alkyl, and R^2 is selected from pyridyl, phenyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, thiazolyl and furanyl.

13. A compound having the formula:



or a pharmaceutically acceptable salt thereof, wherein

A^1 is a member selected from the group consisting of (C_5-C_{12})monocycloalkyl, (C_5-C_{12})heteromonocycloalkyl, (C_8-C_{18})bicycloalkyl, (C_8-C_{18})tricycloalkyl, (C_8-C_{18})heterobicycloalkyl and (C_8-C_{18})heterotricycloalkyl;

R^{11} is a member selected from the group consisting of (C_3-C_{12})alkyl, aryl, aryl(C_1-C_8)alkyl, aryl(C_2-C_8)heteroalkyl, (C_3-C_{12})heteroalkyl, heteroaryl, heteroaryl(C_1-C_8)alkyl and heteroaryl(C_2-C_8)heteroalkyl; and

R^{21} is a member selected from the group consisting of aryl, heteroaryl, aryl(C_1-C_8)alkyl, heteroaryl(C_1-C_8)alkyl, aryl(C_2-C_8)heteroalkyl and heteroaryl(C_2-C_8)heteroalkyl;

and wherein R^{11} and R^{21} can be combined with the nitrogen atom to which each is attached to form a five- to eight-membered ring, with the following provisos:

when R^{21} is 2-pyridyl, R^{11} is other than a substituted or unsubstituted 2-(1-piperazinyl)ethyl or (tetrahydro-2H-pyrido[3,4-b]indol-2-yl)ethyl group;

when R^{21} is substituted or unsubstituted phenyl, R^{11} and R^{21} are not combined to form a ring with the attached nitrogen atom; and

when R^{21} is substituted or unsubstituted phenyl, R^{11} is not allyl, 2-(acylamino)ethyl, or benzyloxycarbonyl.

14. A compound in accordance with claim **13**, wherein A^1 is selected from the group consisting of $(C_8\text{-}C_{18})$bicycloalkyl, $(C_8\text{-}C_{18})$tricycloalkyl, $(C_8\text{-}C_{18})$heterobicycloalkyl and $(C_8\text{-}C_{18})$heterotricycloalkyl.

15. A compound in accordance with claim **13**, wherein A^1 is adamantyl.

16. A compound in accordance with claim **13**, wherein R^{11} is selected from aryl$(C_1\text{-}C_8)$alkyl and heteroaryl$(C_1\text{-}C_8)$alkyl.

17. A compound in accordance with claim **13**, wherein R^{21} is selected from aryl and heteroaryl.

18. A compound in accordance with claim **13**, wherein A^1 is adamantyl, R^{11} is selected from aryl$(C_1\text{-}C_8)$alkyl and heteroaryl$(C_1\text{-}C_8)$alkyl and R^{21} is selected from aryl and heteroaryl.

19. A compound in accordance with claim **13**, wherein A^1 is adamantyl, R^{11} is selected from heteroaryl$(C_3\text{-}C_8)$alkenyl and R^{21} is selected from phenyl and pyridyl.

20. A compound in accordance with claim **13**, wherein A^1 is adamantyl, R^{11} is selected from branched $(C_3\text{-}C_8)$alkyl and R^{21} is selected from phenyl and pyridyl.

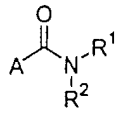
21. A compound in accordance with claim **13**, wherein A^1 is adamantyl, R^{11} is heteroaryl(branched $C_2\text{-}C_8$)alkyl and R^{21} is selected from aryl and heteroaryl.

22. A compound in accordance with claim **13**, wherein A^1 is adamantyl, R^{11} is 1-(heteroaryl)-$(C_2\text{-}C_8)$alkyl and R^{21} is selected from aryl and heteroaryl.

23. A compound in accordance with claim **13**, wherein A^1 is 1-adamantyl, R^{11} is selected from aryl$(C_1\text{-}C_8)$alkyl and heteroaryl$(C_1\text{-}C_8)$alkyl, and R^{21} is selected from pyridyl, phenyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, thiazolyl and furanyl.

24. A method for modulation of LXR in a cell, said method comprising administering to said cell a composition in accordance with claim 1.

25. A method for the treatment of LXR-responsive diseases, comprising administering to a subject in need of said treatment, a compound having the formula:



or a pharmaceutically acceptable salt thereof, wherein

A is a member selected from the group consisting of (C_5-C_{18})alkyl and (C_5-C_{18})heteroalkyl;

R^1 is a member selected from the group consisting of (C_3-C_{12})alkyl, aryl, aryl(C_1-C_8)alkyl, aryl(C_2-C_8)heteroalkyl, (C_3-C_{12})heteroalkyl, heteroaryl, heteroaryl(C_1-C_8)alkyl and heteroaryl(C_2-C_8)heteroalkyl; and

R^2 is a member selected from the group consisting of aryl, heteroaryl, aryl(C_1-C_8)alkyl, heteroaryl(C_1-C_8)alkyl, aryl(C_2-C_8)heteroalkyl and heteroaryl(C_2-C_8)heteroalkyl;

wherein R^1 and R^2 are optionally combined together with the nitrogen atom to which each is attached to form a 5-, 6-, 7- or 8-membered ring, and said compound binds to the ligand binding domain of LXRα with an affinity of at least 1 micromolar.

26. A method in accordance with claim **25**, wherein said disease is selected from the group consisting of hypercholesterolemia and atherosclerosis or other disorders associated with bile acid and cholesterol metabolism.

27. A method in accordance with claim **25**, wherein said compound is administered in conjunction with an additional hypercholesterolemic agent selected from the group consisting of bile acid sequestrants, nicotinic acid, fibric acid derivatives and HMG CoA reductase inhibitors.

INTERNATIONAL SEARCH REPORT

Intern· ıal Application No
PCT/US 00/03806

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D405/12 C07D307/52 C07C233/58 A61K31/443 A61K31/341
A61K31/167 A61P3/10

According to international Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07C A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, CHEM ABS Data, BEILSTEIN Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 54759 A (TULARIK INC., USA) 21 September 2000 (2000-09-21) abstract; claims 1,20; figures 1,2 page 87 -page 88; examples 18.16-18.19 page 89; example 18.21 page 96 -page 97; examples 18.36,19	1-27
X	WO 00 26186 A (YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD., JAPAN) 11 May 2000 (2000-05-11) abstract page 31 page 51 -page 58	1-27
Y	DE 44 38 020 A (THOMAE GMBH DR K) 2 May 1996 (1996-05-02) abstract; claims	1,13

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 October 2000	03/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Paisdor, B

2

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	DE 44 37 999 A (THOMAE GMBH DR K) 2 May 1996 (1996-05-02) abstract; claims page 34; example 10	1,13
X	WO 99 44987 A (ALANEX CORP., USA) 10 September 1999 (1999-09-10) page 11 -page 19; claim 1; examples 10,33,37	13
X	WO 99 40064 A (HOECHST MARION ROUSSEL DEUTSCHLAND G.M.B.H., GERMANY) 12 August 1999 (1999-08-12) claim 1; examples 13-18	13
X	WO 99 06382 A (RECORDATI S.A., CHEMICAL AND PHARMACEUTICAL COMPANY, SWITZ.;RECORDATI) 11 February 1999 (1999-02-11) page 16 -page 25; claim 1; examples	13
X	WO 97 31637 A (RECORDATI S.A., CHEMICAL AND PHARMACEUTICAL CO., SWITZ.;RECORDATI INDU) 4 September 1997 (1997-09-04) page 21; example 3	13
X	WO 94 21611 A (WYETH, JOHN, AND BROTHER LTD., UK) 29 September 1994 (1994-09-29) abstract page 11 -page 14; examples	13
X	BECKWITH, ATHELSTAN L. J. ET AL: "Tandem radical translocation and homolytic aromatic substitution: a convenient and efficient route to oxindoles" J. CHEM. SOC., CHEM. COMMUN. (1995), (9), 977-8 , XP002915029 page 977; examples 6E,8E	13
X	LE BLANC, SYLVIE ET AL: "New access to spiranic.beta.-lactams" TETRAHEDRON LETT. (1992), 33(15), 1993-6 , XP000952843 page 1994; table page 1995; examples 7,9,11	13
X	IKEDA, MASAZUMI ET AL: "Photochemistry of 2-(N-acyl-N-alkylamino)-2-cyclohexenones: formation of spiro-.beta.-lactams" CHEM. PHARM. BULL. (1986), 34(12), 4997-5004 , XP000952842 page 4998; table 1	13

-/--

2

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	IKEDA, MASAZUMI ET AL: "Photochemical synthesis of spiro-.beta.-lactams" J. CHEM. SOC., CHEM. COMMUN. (1984), (12), 758-9 , XP000952858 page 759; table 1 ---	13
X	EP 0 019 745 A (BASF A.-G., FED. REP. GER.) 10 December 1980 (1980-12-10) page 29; examples 42,43 claim 1 page 31 -page 32; examples 59,70 ---	13
X	EP 0 023 669 A (BAYER A.-G., FED. REP. GER.) 11 February 1981 (1981-02-11) page 27; claims; table ---	13
X	EP 0 013 360 A (BASF A.-G., FED. REP. GER.) 23 July 1980 (1980-07-23) page 35; examples 289,290 page 30; examples 385,386 claim 1 ---	13
X	EP 0 012 428 A (BASF A.-G., FED. REP. GER.) 25 June 1980 (1980-06-25) page 10, line 11 - line 15 page 17; examples 35,36 claim 1 ---	13
X	DE 26 25 227 A (LILLY INDUSTRIES LTD., ENGL.) 23 December 1976 (1976-12-23) page 2 -page 3; claim 1 examples 5-7,10,13-16,18,36 claim 1 ---	13
X	DE 26 25 242 A (LILLY INDUSTRIES LTD., ENGL.) 23 December 1976 (1976-12-23) claim 1 page 16; example 4 page 18, paragraph 10 page 19, paragraphs 2,4 page 20 -page 22; examples 37,38,41,44,45 page 31 -page 32; examples 62-64 page 37; example 89 ---	13
X	DE 25 15 113 A (CIBA-GEIGY A.-G., SWITZ.) 23 October 1975 (1975-10-23) page 1 page 16 -page 17; examples 82-95 page 19; example 113 ---	13
X	US 4 204 002 A (HUBELE, ADOLF) 20 May 1980 (1980-05-20) column 13 -column 16; examples 82-95 ---	13

-/--

2

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/US 00/03806

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 1995, no. 10, 30 November 1995 (1995-11-30) -& JP 07 188215 A (MEIJI SEIKA KAISHA LTD), 25 July 1995 (1995-07-25) abstract page 2, column 2; figure VI; examples ---	13
X	PATENT ABSTRACTS OF JAPAN vol. 1995, no. 06, 31 July 1995 (1995-07-31) -& JP 07 056392 A (MITSUI TOATSU CHEM INC), 3 March 1995 (1995-03-03) abstract page 6; example 17; table 1 page 9; example 51; table 2 ---	13
X	PATENT ABSTRACTS OF JAPAN vol. 012, no. 230 (C-508), 29 June 1988 (1988-06-29) -& JP 63 023822 A (TOKUYAMA SODA CO LTD), 1 February 1988 (1988-02-01) abstract page 11; example 52; table 1 -----	13

2

INTERNATIONAL SEARCH REPORT

. ormation on patent family members

Interna al Application No
PCT/US 00/03806

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0054759 59 A		NONE	
WO 0026186 86 A		NONE	
DE 4438020 A	02-05-1996	NONE	
DE 4437999 A	02-05-1996	NONE	
WO 9944987 A	10-09-1999	AU 2885399 A	20-09-1999
WO 9940064 A	12-08-1999	DE 19804251 A	05-08-1999
		AU 3139899 A	23-08-1999
WO 9906382 A	11-02-1999	IT MI971862 A	01-02-1999
		IT MI971863 A	01-02-1999
		AU 9256498 A	22-02-1999
		EP 1000045 A	17-05-2000
WO 9731637 A	04-09-1997	IT MI960378 A	28-08-1997
		AU 2093297 A	16-09-1997
		EP 0906100 A	07-04-1999
		US 5990114 A	23-11-1999
WO 9421611 A	29-09-1994	AU 6149094 A	11-10-1994
		EP 0689534 A	03-01-1996
		JP 8507779 T	20-08-1996
		US 5629323 A	13-05-1997
		ZA 9401739 A	11-09-1995
EP 0019745 A	10-12-1980	DE 2920435 A	04-12-1980
		AT 1361 T	15-08-1982
		AU 5851480 A	27-11-1980
		CA 1127168 A	06-07-1982
		CS 215060 B	30-07-1982
		DD 150842 A	23-09-1981
		DE 3060697 D	16-09-1982
		DK 214580 A	20-11-1980
		JP 55160753 A	13-12-1980
		NZ 193694 A	07-09-1982
		PL 224310 A	13-02-1981
		ZA 8002942 A	24-06-1981
EP 0023669 A	11-02-1981	DE 2931640 A	19-02-1981
		AR 224904 A	29-01-1982
		AT 1522 T	15-09-1982
		AU 6099280 A	05-02-1981
		BR 8004839 A	10-02-1981
		CA 1133510 A	12-10-1982
		CS 214753 B	28-05-1982
		DD 154666 A	14-04-1982
		DE 3060826 D	28-10-1982
		DK 333980 A	04-02-1981
		ES 493953 D	16-05-1981
		ES 8105271 A	16-08-1981
		HU 184315 B	28-08-1984
		IL 60729 A	31-10-1983
		JP 56026857 A	16-03-1981
		NZ 194511 A	25-05-1982

INTERNATIONAL SEARCH REPORT

...ormation on patent family members

Interna... al Application No
PCT/US 00/03806

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 0023669 A		PL	226010 A	27-11-1981
		PT	71602 A	01-08-1980
		SU	915778 A	23-03-1982
		ZA	8004707 A	26-08-1981
EP 0013360 A	23-07-1980	DE	2854598 A	03-07-1980
		AT	821 T	15-04-1982
		AU	5385779 A	26-06-1980
		BR	7908221 A	23-09-1980
		CS	214681 B	28-05-1982
		DD	147992 A	06-05-1981
		DE	2962483 D	19-05-1982
		DK	536679 A	19-06-1980
		JP	55092374 A	12-07-1980
		NZ	192428 A	09-03-1982
		PL	220417 A	15-12-1980
		SU	906346 A	15-02-1982
		ZA	7906831 A	31-12-1980
EP 0012428 A	25-06-1980	DE	2854600 A	26-06-1980
		AT	64 T	15-05-1981
		AU	5385479 A	26-06-1980
		BR	7908263 A	23-09-1980
		CA	1117131 A	26-01-1982
		CS	212332 B	26-03-1982
		DD	147807 A	22-04-1981
		DE	2960357 D	20-08-1981
		DK	536779 A	19-06-1980
		IE	49237 B	04-09-1985
		JP	55085558 A	27-06-1980
		NZ	192429 A	13-07-1981
		PL	220416 A	15-12-1980
		US	4235928 A	25-11-1980
		ZA	7906788 A	31-12-1980
DE 2625227 A	23-12-1976	GB	1547564 A	20-06-1979
		AR	219280 A	15-08-1980
		AR	217662 A	15-04-1980
		AT	355562 B	10-03-1980
		AT	412376 A	15-08-1979
		AU	506564 B	10-01-1980
		AU	1461876 A	08-12-1977
		BE	842578 A	03-12-1976
		BG	26515 A	12-04-1979
		BG	25211 A	10-08-1978
		CA	1081219 A	08-07-1980
		CH	622254 A	31-03-1981
		CH	618972 A	29-08-1980
		CS	219320 B	25-03-1983
		CS	219321 B	25-03-1983
		DD	125206 A	06-04-1977
		DK	243576 A	06-12-1976
		ES	448477 A	01-11-1977
		ES	460711 A	16-04-1978
		FR	2313046 A	31-12-1976
		GR	60336 A	09-05-1978
		HU	174190 B	28-11-1979
		IE	43579 B	08-04-1981

INTERNATIONAL SEARCH REPORT

...ormation on patent family members

Intern ...al Application No
PCT/US 00/03806

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 2625227 A		IL 49691 A	16-09-1980
		JP 51146465 A	16-12-1976
		MX 3638 E	13-04-1981
		NL 7606179 A	07-12-1976
		NZ 181010 A	28-04-1978
		PH 14627 A	12-10-1981
		PT 65180 A,B	01-07-1976
		RO 70771 A	03-08-1983
		SE 431646 B	20-02-1984
		SE 7606225 A	06-12-1976
		SU 648094 A	15-02-1979
		SU 654168 A	25-03-1979
		US 4186204 A	29-01-1980
		US 4166123 A	28-08-1979
		US 4089962 A	16-05-1978
		YU 123376 A	31-10-1982
		YU 137276 A	31-10-1982
		ZA 7603210 A	25-01-1978
DE 2625242 A	23-12-1976	GB 1548398 A	11-07-1979
		AR 214974 A	31-08-1979
		AT 355011 B	11-02-1980
		AT 412476 A	15-07-1979
		AU 505603 B	29-11-1979
		AU 1462076 A	08-12-1977
		BE 842577 A	03-12-1976
		BG 27358 A	12-10-1979
		CA 1090794 A	02-12-1980
		CH 616660 A	15-04-1980
		CS 189771 B	30-04-1979
		DD 125076 A	30-03-1977
		DK 243476 A	06-12-1976
		ES 448588 A	16-07-1977
		FR 2313032 A	31-12-1976
		GR 60435 A	26-05-1978
		HU 177338 B	28-09-1981
		IE 43473 B	11-03-1981
		IL 49690 A	31-03-1980
		JP 51149264 A	22-12-1976
		MX 3637 E	13-04-1981
		NL 7606120 A	07-12-1976
		NZ 181009 A	11-01-1979
		PH 14688 A	10-11-1981
		PH 15711 A	14-03-1983
		PH 16022 A	30-05-1983
		PT 65181 A,B	01-07-1976
		RO 70686 A	09-09-1982
		SE 426591 B	31-01-1983
		SE 7606224 A	06-12-1976
		SU 655313 A	30-03-1979
		US 4222946 A	16-09-1980
		US 4082771 A	04-04-1978
		US 4088773 A	09-05-1978
		US 4187232 A	05-02-1980
		YU 137076 A	31-10-1982
		ZA 7602363 A	25-05-1977
DE 2515113 A	23-10-1975	CH 604510 A	15-09-1978

INTERNATIONAL SEARCH REPORT

...rmation on patent family members

Internr al Application No
PCT/US 00/03806

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 2515113 A		CH 593612 A	15-12-1977
		AR 231053 A	28-09-1984
		AT 343955 B	26-06-1978
		AT 263975 A	15-10-1977
		AU 7994675 A	14-10-1976
		BG 24934 A	15-06-1978
		CA 1067909 A	11-12-1979
		CS 187469 B	31-01-1979
		DD 118978 A	05-04-1976
		DK 136275 A,B,	10-10-1975
		EG 11894 A	31-12-1977
		ES 436384 A	01-04-1977
		FI 750923 A,B,	10-10-1975
		FR 2267310 A	07-11-1975
		GB 1500576 A	08-02-1978
		HU 175063 B	28-05-1980
		IE 41108 B	24-10-1979
		IL 47045 A	31-01-1979
		JP 1263084 C	16-05-1985
		JP 50140633 A	11-11-1975
		JP 59039401 B	22-09-1984
		LU 72225 A	02-03-1976
		MC 1089 A	22-11-1976
		NL 7503767 A	13-10-1975
		NO 751083 A,B,	10-10-1975
		OA 4923 A	31-10-1980
		PH 11564 A	31-03-1978
		SE 429917 B	10-10-1983
		SE 7503520 A	10-10-1975
		TR 18772 A	23-08-1977
		US 4093738 A	06-06-1978
		US 4204002 A	20-05-1980
		YU 89475 A	27-04-1983
		BE 827672 A	08-10-1975
		SU 793354 A	30-12-1980
		ZA 7502224 A	25-02-1976
US 4204002 A	20-05-1980	CH 604510 A	15-09-1978
		CH 593612 A	15-12-1977
		AR 231053 A	28-09-1984
		AT 343955 B	26-06-1978
		AT 263975 A	15-10-1977
		AU 7994675 A	14-10-1976
		BG 24934 A	15-06-1978
		CA 1067909 A	11-12-1979
		CS 187469 B	31-01-1979
		DD 118978 A	05-04-1976
		DE 2515113 A	23-10-1975
		DK 136275 A,B,	10-10-1975
		EG 11894 A	31-12-1977
		ES 436384 A	01-04-1977
		FI 750923 A,B,	10-10-1975
		FR 2267310 A	07-11-1975
		GB 1500576 A	08-02-1978
		HU 175063 B	28-05-1980
		IE 41108 B	24-10-1979
		IL 47045 A	31-01-1979
		JP 1263084 C	16-05-1985

INTERNATIONAL SEARCH REPORT

...ormation on patent family members

Internal Application No
PCT/US 00/03806

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4204002 A		JP 50140633 A	11-11-1975
		JP 59039401 B	22-09-1984
		LU 72225 A	02-03-1976
		MC 1089 A	22-11-1976
		NL 7503767 A	13-10-1975
		NO 751083 A,B,	10-10-1975
		OA 4923 A	31-10-1980
		PH 11564 A	31-03-1978
		SE 429917 B	10-10-1983
		SE 7503520 A	10-10-1975
		TR 18772 A	23-08-1977
		US 4093738 A	06-06-1978
		YU 89475 A	27-04-1983
		BE 827672 A	08-10-1975
		SU 793354 A	30-12-1980
		ZA 7502224 A	25-02-1976
JP 07188215 A	25-07-1995	NONE	
JP 07056392 A	03-03-1995	NONE	
JP 63023822 A	01-02-1988	JP 1845314 C	25-05-1994
		JP 5055489 B	17-08-1993